SCIENTIFIC ARCHIVES.COM

Arch Gastroenterol Res. 2023;4(1):36-42.

Archives of Gastroenterology Research | Opinion

Blastocystosis and Urticaria: An Overview from a Syndemic Perspective

Luis Fonte Galindo[1,*], Yamilé Aleaga Santiesteban[2], María Ginori Gilke[3], Yosiel Molina[4], Yisel Hernández Barrios[5]

[1]Department of Parasitology, Institute of Tropical Medicine "Pedro Kourí, Havana 11 400, Cuba

[2]Department of Clinical Microbiology Diagnostic, Institute of Tropical Medicine "Pedro Kourí", Havana 11 400, Cuba

[3]Department of Teaching, Polyclinic "Plaza de la Revolución", Havana 11300, Cuba

[4]Section of International Relations, Institute of Tropical Medicine "Pedro Kourí, Havana 11400, Cuba

[5]Department of Vector Control, Institute of Tropical Medicine "Pedro Kourí, Havana 11400, Cuba

[*]Correspondence should be addressed to Luis Fonte Galindo, luisfonte@infomed.sld.cu

Received date: November 17, 2023, **Accepted date:** December 06, 2023

Citation: Fonte Galindo L, Aleaga Santiesteban Y, Ginori Gilke M, Molina Y, Hernández Barrios Y. Blastocystosis and Urticaria: An Overview from a Syndemic Perspective. Arch Gastroenterol Res. 2023;4(1):36-42.

Abstract

Numerous studies have found an association between infection by some species of intestinal parasites and the development of urticarial lesions. In this document we have commented on the published findings that show the association between infection by *Blastocystis* spp. and urticaria, and on the theorizations in relation to the mechanisms that would explain it.

Due to sharing risk factors and transmission ways, there is a marked geographic coincidence among intestinal parasitic infections. In fact, polyparasitism is a common phenomenon in low- and middle-income countries in Sub-Saharan Africa, Asia, Latin America, and the Caribbean where infections by protozoa and intestinal helminths are endemic. This argument, among others, suggest that the epidemiological and healthcare approach to urticaria associated with infection by *Blastocystis* spp. should be done from a syndemic approach that takes into account the ways in which social environments contribute to intestinal parasite infections clustering, the pathways through which those infections could interact biologically in each individual influencing the development and evolution of urticarial lesions, and the ways in which those interactions complicate diagnosis and treatment.

Keywords: *Blastocystis* spp., Blastocystosis, Urticaria, Evidence, Mechanisms, Syndemic

Introduction

Intestinal parasitic infections continue to be a major public health problem, especially in low- and middle-income countries [1-3]. It is estimated that those infections affect more than one billion people worldwide [1,2]. *Blastocystis* spp. is the most frequently found protozoan in the feces of humans and other animals [4-6]. Depending on the presence of factors that promote its transmission, the prevalence of infection by *Blastocystis* spp. varies between countries and between communities in each country [6]. It is considered that the prevalence of this parasitism ranges between 30% and 60% in low- and middle-income countries located in the tropical belt of the planet and between 5% and 20% in the rest [6-8].

The care of patients with urticaria, defined this clinical manifestation as a skin rash characterized by dark red evanescent bumps, usually pluriginous, which may be accompanied by angioedema, is a frequent event in universal medical practice [9]. A wide variety of factors, sometimes overlapping, can lead to urticarial lesions. The first report of the association between parasitic infection and urticaria dates back to 1949 [10]. Since then, numerous studies have reported this relation [11-14]. A relatively recent systematic review reported prevalences of parasitic infections in adult and pediatric urticaria patients of 5.4% and 37.8%, respectively [14].

The association between infection by *Blastocystis* spp. and

cutaneous manifestations, particularly urticaria, has been increasingly reported in the international literature [15-19]. To make an approach, from a syndemic perspective to the evidence and possible mechanisms linking *Blastocystis* spp. to the development of urticarial lesions is the purpose of this article.

Blastocystis spp. and Blastocistosis

The term blastocystosis, in its broadest sense, refers to the human infection caused by *Blastocystis* spp., regardless of whether or not it gives rise to clinical manifestations [20]. As in the cases of other infections, the development of signs and symptoms attributable to this parasitism depends on the interaction of factors related to the host, the protozoan and the environment, aspects that are currently subject of intense scrutiny.

Blastocystis spp., an anaerobic protozoan classified within the phylum Stramenopiles, includes a heterogeneous set of subtypes (ST) that present extensive pleomorphism and different replication strategies [21,22]. Four classic forms of the microorganism have been described in feces and *in vitro* cultures: vacuolar, granular, amoeboid, and cystic [23]. Other rarer forms have also been reported: avacuolar and multivacuolar [6]. The cyst is the infecting form, and the transmission occurs mainly through the fecal-oral via contaminated water and food [6].

The pathogenic nature of *Blastocystis* spp. has been subject of debate for a long time [6,7,23,24]. The finding of this protozoan in the feces of asymptomatic individuals has been a basis for disputing its pathogenicity [23]. However, clinical, phenotypic, and genotypic evidence accumulated in recent years suggests that *Blastocystis* spp. comprises a group of morphologically indistinguishable microorganisms, made up of numerous STs that, depending on the relationship they establish with their respective hosts, show different degrees of virulence [7,16,19,25,26]. The prevalence of blastocystosis, an entity that was barely reported four decades ago, has increased rapidly in recent years [6,24]. The growing certainty about the pathogenicity of *Blastocystis* spp., which has obviously led to more attention being paid to its detection, could have contributed to the increase in the prevalence figures of this parasitism. Furthermore, there is increasing evidence that humans are not the exclusive host of *Blastocystis* spp. Blastocystosis is considered a zoonosis with several STs of the parasite being identified in other mammals, birds, reptiles, amphibians, and insects [27].

According to the sequence analysis of the ribonucleic acid gene of the minor ribosomal subunit, at least 26 STs of *Blastocystis* spp. have been reported in both humans and other animals [28,29]. In humans, STs 1-9 and ST12 have been found [30,31]; some of which have also been observed in animals, such as ST3 in non-human primates, ST5 in cattle and pigs, ST7 in birds, and ST8 in non-human primates and birds [32,33]. On the contrary, some STs such as ST10 and ST14 circulate in other animals and have never been described in human infections [34]. Simultaneous colonization with different STs is not uncommon [35]. Regarding the existence of STs 18 to 26, and others reported later, there is no definitive evidence, and some researchers believe that, to some extent, they could be molecular chimeras [36].

Evidence of the Association between Blastocystosis and Urticaria

The association between urticaria and infectious entities has been reported and not always categorically demonstrated. Of them, the best documented are: among viruses, with hepatitis B and herpes simplex [37]; among bacteria, with *Helicobacter pylori*, *Mycobacterium tuberculosis*, *Streptococcus* spp., and *Mycoplasma* spp. [37,38]; among fungi, with onychomycosis, tinea pedis and *Candida* spp. [39]; among helminths, with *Strongyloides stercoralis* [40]; and among protozoa, with *Giardia lamblia* and *Entamoeba histolytica* and, more recently, with *Blastocystis* spp. [6,16,19,24,40].

The data from the reviewed literature allow us to affirm that urticaria is the most frequent cutaneous manifestation associated with infection by *Blastocystis* spp. [6,19,24,37-50]. Most of the works carried out to demonstrate the link between suffering from blastocystosis and developing urticaria, especially those carried out in series with adequate sample sizes, succeeded to demonstrate the relation [6,19,24,44-46,48,49]. Other studies, generally reports of individual cases or very small series, could not confirm the association [41-43].

When attempts were made to demonstrate the association by studying the response of urticarial lesions to treatment against the protozoan, numerous studies found the disappearance of these manifestations after the administration of the drug [19,51,52], and only two papers reported the continuation and/or the reappearance of the lesions in some of the treated patients [50,53]. In our opinion, the results of these two works do not negate the aforementioned association, but rather alert us to take into account other causes of urticaria at play in the same scenery.

During the last five decades, the possible relationship between *Blastocystis* STs and some pathological manifestations has been the subject of intense controversy. Clark, in a paradigmatic work published in 1997, was pioneer in suggesting this type of link [54]. Since then, numerous publications have reported on the association between *Blastocystis* STs and clinical manifestations, both digestive and extraintestinal [6,41,42,44,45,47,55-60]. Several works found that the amoeboid form of some STs was related to the development of urticarial lesions [16,19,44].

A very recent study, which delved into the alleles of the STs present, showed that ST3, and to a lesser extent STs 2 and 1, in that order, were the most frequently found in individuals infected by *Blastocystis* spp. who suffered from urticarial lesions. However, and this was the most novel finding of this work, only allele 34 of ST3 showed a statistically significant association with the development of urticaria when compared with a control group [6]. The authors of this research conclude that allele 34 of ST3 is related to the pathogenic mechanisms that characterize the allergic reaction of urticarial lesions, to which we will refer in the next section of this article.

It is worth mentioning that the association between infection by *Blastocystis* spp. and non-urticarial skin manifestations has also been reported; for example, with papules, rash, palmoplantar or diffuse pruritus, and atopic dermatitis [5,16,19,44,46-48]. Regarding these associations, the available documentation is very scarce and mostly anecdotal. Almost all of the works that report them are based on individual cases, or very small series, in which the healing of the lesions after treating the infection by *Blastocystis* spp. has been the main argument mentioned. In our opinion, these possible associations have yet to be demonstrated.

Biological Mechanisms Underlying the Association between Blastocystosis and Urticaria

In relation to the processes by which infection by *Blastocystis* spp. would lead to the development of urticarial lesions, the available information is not conclusive and, in many aspects, too speculative. Three mechanisms, not exclusive and possibly interacting, are the most frequently mentioned:

Development of type I hypersensitivity phenomena

According to this mechanism, also described for urticarial manifestations associated with infection by other parasites (for example, *G. lamblia*), mast cells at the site of the lesions would degranulate when interacting with the Fc regions of IgE antibodies directed against *Blastocystis* spp. antigens, or against others coming from the intestinal lumen, which would reach the bloodstream due to the intestinal permeability disorders that occur in this parasitism. Soluble mediators released by the degranulation of mast cells, histamine in the first place, would be ultimately responsible for dermatological lesions. Various types of evidence favor the acceptance of this mechanism as a trigger for urticaria in blastocystosis patients: (i) the amoeboid form of ST3, the most frequently related to the development of urticarial lesions, is the one that best adheres to the intestinal epithelium and, consequently, the one that could most damage its permeability [14,48,61,62]; (ii) the entry of parasite antigens through the intestinal mucosa induces the activation of Th2 lymphocyte clones and with it the production of cytokines such as interleukin 3 (IL-3), IL-4, IL-5, and IL-13 [6,14], high titers of total and specific IgE [6,41], and increased numbers of circulating eosinophils [41,48,63]; (iii) the interaction of the FceR1 receptors of mast cells with the Fc ends of circulating IgE-*Blastocystis* antigen complexes induce degranulation of these cells [48,49,64].

Modifications in the composition of the intestinal microbiome

In the reviewed literature, the possible involvement of the intestinal microbiome in the development of diseases is a relatively recent topic [65]. In harmony with this general consideration, Nabizadeh et al., in 2017, and Stensvold and van der Giezen, in 2018, anticipated that the microbiome could be playing a pathogenic role in human infection with *Blastocystis* spp. [66,67]. In support of this opinion, an evaluation of the composition of the digestive microbiome in stool samples from patients with chronic urticaria and healthy individuals revealed that the relative amount of bacteria of the Enterobacteriaceae family in the former was greater than that in the latter; on the other hand, the frequencies of *Akkermansia muciniphila*, *Clostridium leptum* and *Faecalibacterium prausnitzii* in healthy individuals were significantly higher than those recorded in patients with chronic urticaria [66]. Another study carried out in China, demonstrated a higher frequency of the pathogenic bacteria *Escherichia coli* than of the bacteria *F. prausnitzii*, *Prevotella copri*, and *Bacteroides* spp. in urticaria patients than in healthy controls [68].

Changes in the expression profiles of circulating micro ribonucleic acids

Micro ribonucleic acids (miRNAs) are small-sized (20 to 23 nucleotides), endogenous and non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Circulating miRNAs can be found in various body fluids such as serum, plasma, saliva, etc. and can show modified expression profiles in many biological processes, including diseases [19]. Some studies have explored changes in miRNA profiles, and their possible pathogenic significance, in skin diseases [69]. A very recent work examined these profiles in patients of urticaria, which were grouped as infected or not by *Blastocystis* spp. and in healthy individuals, who were also grouped as infected or not by this parasite. The study found that urticaria patients infected by *Blastocystis* spp. had decreased levels of some miRNAs relative to members of the other groups. This research also found that people who did not suffer from hives and were infected with the protozoan showed elevated levels of other miRNAs relative to members of the other groups. The authors of this research, in addition to demonstrating the occurrence of specific changes in the expression profiles of circulating miRNAs in people infected by *Blastocystis* spp. who suffer from urticarial lesions, suggested delving into the molecular mechanisms by which the elevation of the levels of certain circulating miRNAs would be linked to the dermatological lesions [24].

Necessity of a Syndemic Approach to the Handle of Urticaria Associated to Blastocystosis

The conventional approach to health conception and clinical practice assumes the disease as a distinct entity in nature, separating it from factors such as other diseases and the social context in which they are found. However, increasing evidence demonstrates that those factors tend to interact in various and consequential ways, having a substantial impact on the health of individuals and whole populations. Taking into account those interactions, a more holistic approach, known as syndemic, has emerged during the last three decades [70-73]. Singer et al. refer to this relatively novel methodology in this inclusive form "Specifically, a syndemic approach examines why certain diseases cluster (ie, multiple diseases affecting individuals and groups); the pathways through which they interact biologically in individuals and within populations, and thereby multiply their overall disease burden, and the ways in which social environments, specially conditions of social inequality and injustice, contribute to disease clustering and interactions as well as to vulnerability" [72]. The recognition of syndemic interactions in medical practice has considerable importance for the better understanding of the clinical presentation of patients, the correct diagnosis and treatment of the different diseases that they could be suffering from, and the appropriate decision-making in terms of health policy.

Due to sharing risk factors and transmission ways, there is a marked geographic coincidence among intestinal parasitic infections. In fact, polyparasitism is a common phenomenon in low- and middle-income countries in sub-Saharan Africa, Asia, Latin America, and the Caribbean where infections by protozoa and intestinal helminths are endemic [3]. Under these circumstances, the epidemiological and healthcare approach to the handling of urticarial lesions associated with parasitic infections, including those related to *Blastocystis* spp. infection, must be done from a syndemic perspective. Such an approach should not only take into account the common socioeconomic and health conditions that favor the transmission of more than one species, with the consequent parasite comorbidity, but also consider the possible enhancing effect of the pathogenic mechanisms of one species on those of another. Moreover, it should address the diagnostic and therapeutic challenges arising from the presence of various species in a single patient. For example, *Blastocystis* spp. and *G. lamblia*, frequently found in coinfections in endemic areas, are the intestinal parasites most frequently associated with urticaria, and both, as part of their pathogenic mechanisms, increase intestinal permeability and, allowing the passage of parasitic antigens into the bloodstream, thereby enhancing the development of urticarial lesions.

Conclusions

Due to their profound impact on human well-being and development, intestinal parasitic infections continue to be an important public health problem, especially in low- and middle-income countries [1,2]. Among the intestinal parasitisms caused by protozoa, infection by *Blastocystis* spp., is the most frequently detected in humans [4-6].

Numerous studies have found an association between infection by some species of intestinal parasites and the development of urticarial lesions [11-14]. After reviewing what has been published on the subject, in this article we have commented on the findings that show the association between infection by *Blastocystis* spp. and urticaria, and on the theorizations in relation to the mechanisms that would explain it.

Taking into consideration the arguments presented above, and as has already been suggested for other coexistent infectious diseases in other settings [72], the epidemiological and healthcare approach to urticaria associated with infection by *Blastocystis* spp. should be done from a syndemic approach that takes into account the ways in which social environments contribute to intestinal parasite infections clustering, the pathways through which those infections could interact biologically in each individual influencing the development and evolution of urticarial lesions, and the ways in which those interactions complicate diagnosis and treatment.

Author Contribution Statement

Luis Fonte wrote the first version of the manuscript; all authors reviewed, edited, and approved the final version for submission.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Bisetegn H, Debash H, Ebrahim H, Erkihun Y, Tilahun M, Feleke DG. Prevalence and determinant factors of intestinal parasitic infections and undernutrition among primary school children in North-Central Ethiopia: A school-based cross-sectional study. J Parasitol Res. 2023;2023:1-10.

2. World Health Organization. Global report on neglected tropical diseases. Geneva: WHO; 2023 [acceso 2/08/2023]. Disponible en: https://www.who.int/teams/control-of-neglected-tropical-diseases/global-report-on-neglected-tropical-diseases-2023

3. Hailu GG, Ayele ET. Assessment of the prevalence of intestinal parasitic infections and associated habit and culture-related risk factors among primary schoolchildren in Debre Berhan town, Northeast Ethiopia. BMC Public Health. 2021;21:112.

4. Stensvold CR, Kevin SW, Tan C, Clark G. *Blastocystis*. Trends Parasitol. 2020;36:315-6.

5. Deng L, Wojciech L, Gascoigne NRJ, Peng G, Tan KSW. New insights into the interactions between *Blastocystis*, the gut microbiota, and host immunity. PLoS Pathog. 2021;17:e1009253.

6. Aykur M, Camyar A, Türk BG, Sin AZ, Dagci H. Evaluation of association with subtypes and alleles of *Blastocystis* with chronic spontaneous urticaria. Acta Trop. 2022;231:106455.

7. Tan KS. New insights on classification, identification, and clinical relevance of *Blastocystis* spp. Clin Microbiol Rev. 2008;21:639-65.

8. Khorshidvand Z, Khazaei S, Amiri M, Taherkhani H, Mirzaei A. Worldwide prevalence of emerging parasite *Blastocystis* in immunocompromised patients: A systematic review and meta-analysis. Microbial Pathogenesis. 2021;152:104615.

9. Kayiran MA, Akdeniz N. Diagnosis and treatment of urticaria in primary care. North Clin Istanb. 2019;6:93-9.

10. Harris RH, Mitchell JH. Chronic urticaria due to *Giardia lamblia*. Arch Dermatol Syphilol. 1949;59:587-9.

11. Giacometti A, Cirioni O, Antonicelli L, D'Amato G, Silvestri C, Del Prete MS, et al. Prevalence of intestinal parasites among individuals with allergic skin diseases. J Parasitol. 2003;89:490-2.

12. Bakiri AH, Mingomataj EC. Parasites induced skin allergy: a strategic manipulation of the host immunity. J Clin Med Res. 2010;2:247-55.

13. Caffarelli C, Cuomo B, Cardinale F, Barberi S, Dascola CP, Agostinis F, et al. Aetiological factors associated with chronic urticaria in children: a systematic review. Acta Derm Venereol. 2013;93:268-72.

14. Kolkhir P, Balakirski G, Merk HF, Olisova O, Maurer M. Chronic spontaneous urticaria and internal parasites–a systematic review. Allergy. 2016;71:308-22.

15. Coyle CM, Varughese J, Weiss LM, Tanowitz HB. *Blastocystis*: to treat or not to treat. Clin Infect Dis. 2012;54:105-10.

16. Casero RD, Mongi F, Sanchez A, Ramirez JD. *Blastocystis* and urticaria: Examination of subtypes and morphotypes in an unusual clinical manifestation. Acta Trop. 2015;148:156-61.

17. Andersen LO, Stensvold CR. *Blastocystis* in health and disease: are we moving from a clinical to a public health perspective? J Clin Microbiol. 2016;54:524-8.

18. Cifre S, Gozalbo M, Ortiz V, Soriano JM, Merino JF, Trelis M. *Blastocystis* subtypes and their association with irritable bowel syndrome. Med Hypotheses. 2018;116:4-9.

19. Bahrami F, Babaei E, Badirzadeh A, Riabi TR, Abdoli A. *Blastocystis*, urticaria, and skin disorders: review of the current evidences. Eur J Clin Microbiol Infect Dis. 2020;39:1027-42.

20. Boorom K, Smith H, Nimri L, Viscoglios E, Spanakos G, Parkar U. Oh my aching gut: irritable bowel syndrome, *Blastocystis*, and asymptomatic infection. BMC Parasit Vectors. 2008;1:40.

21. Ruggiero MA, Gordon DP, Orrell TM, Bailly N, Bourgoin T, Brusca RC, et al. A Higher Level Classification of All Living Organisms. PLoS One. 2015;10: e0119248.

22. Deng L, Chai Y, Zhou Z, Liu H, Zhong Z, Hu Y, et al. Epidemiology of *Blastocystis* sp. infection in China: a systematic review. Parasite. 2019;26:41.

23. Meloni D, Sanciu G, Poirier P, El Alaoui H, Chabé M, Viscoglios E. Molecular subtyping of *Blastocystis* sp. Isolates from symptomatic patients in Italy. Parasitol Res. 2011;109:613-9.

24. Örsten S, Baysal İ, Akdoğan N, İnal N, Bostan E, Çiftçi SY, et al. Possible microRNA-based mechanism underlying relationship between chronic spontaneous urticaria and *Blastocystis*. Exp Parasitol. 2023;245:108453.

25. Fonte L, González Z, Fong A, Méndez Y, Moreira Y. Patogenicidad de *Blastocystis* spp. Evidencias y mecanismos. Rev Cubana Med Trop 2014;66. [acceso 20/10/2023]. Disponible en: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=56227

26. Clark CG, van der Giezen M, Alfellani MA, Stensvold CR. Recent developments in *Blastocystis* research. Adv Parasitol. 2013;82:1-32.

27. Mohammadpour I, Bozorg-Ghalati F, Gazzonis AL, Manfredi MT, Hossein M, Motazedian H, et al. First molecular subtyping and phylogeny of *Blastocystis* spp. isolated from domestic and synanthropic animals (dogs, cats and brown rats) in southern Iran. Parasite Vectors. 2020;13:365.

28. Deng L, Yao JX, Liu HF, Zhou ZY, Chai YJ, Wang WY, et al. First report of *Blastocystis* in giant pandas, red pandas, and various bird species in Sichuan province, southwestern China. IJP: Parasites and Wildlife. 2019;9:298-30.

29. Maloney JG, Lombard JE, Urie NJ, Shivley CB, Santin M. Zoonotic and genetically diverse subtypes of *Blastocystis* in US pre-weaned dairy heifer calves. Parasitol Res. 2019;118:575-82.

30. Ramírez JD, Sánchez A, Hernández C, Flórez C, Bernal MC, Giraldo JC, et al. Geographic distribution of human *Blastocystis* subtypes in South America. Infect Genet Evol 2016;41:32-5.

31. Zhang W, Ren G, Zhao W, Yang Z, Shen Y, Sun Y, et al. Genotyping of *Enterocytozoon bieneusi* and subtyping of *Blastocystis* in cancer patients: relationship to diarrhea and assessment of zoonotic transmission. Front Microbiol. 2017;8:1835.

32. Moosavi A, Haghighi A, Mojarad EN, Zayeri F, Alebouyeh M, Khazan H, et al. Genetic variability of *Blastocystis* sp. isolated from symptomatic and asymptomatic individuals in Iran. Parasitol Res. 2012;111:2311-5.

33. Cian A, El Safadi D, Osman M, Moriniere R, Gantois N, Benamrouz-Vanneste S, et al. Molecular epidemiology of *Blastocystis* sp. in various animal groups from two French zoos and evaluation of potential zoonotic risk. PLoS One. 2017;12:e0169659.

34. Stensvold CR, Clark CG. Molecular identification and subtype analysis of *Blastocystis*. Curr Protoc Microbiol. 2016;43:20A.2.1-20A.2.10.

35. Scanlan PD, Stensvold CR, Cotter PD. Development and application of a *Blastocystis* subtype-specific PCR sssay reveals that mixed-subtype infections are common in a healthy human population. Appl Environ Microbiol. 2015;81:4071-6.

36. Stensvold CR, Clark CG. Pre-empting pandora's box: *Blastocystis* subtypes revisited. Trends Parasitol. 2020;36:229-32.

37. Wedi B, Raap U, Kapp A. Chronic urticaria and infections. Curr Opin Allergy Clin Immunol. 2004;4:387-96.

38. Magen E, Mishal J, Schlesinger M, Scharf S. Eradication of *Helicobacter pylori* infection equally improves chronic urticaria with positive and negative autologous serum skin test. Helicobacter. 2007;12:567-71.

39. Staubach P, Vonend A, Burow G, Metz M, Magerl M, Maurer M. Patients with chronic urticaria exhibit increased rates of sensitisation to *Candida albicans*, but not to common moulds. Mycoses. 2009;52:334-8.

40. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol. 2002;23:147-69.

41. Pasqui AL, Savini E, Saletti M, Guzzo C, Puccetti L, Auteri A. Chronic urticaria and *blastocystis hominis* infection: a case report. Eur Rev Med Pharmacol Sci. 2004;8:117-20.

42. Katsarou-Katsari A, Vassalos CM, Tzanetou K, Spanakos G, Papadopoulou C, Vakalis N. Acute urticaria associated with amoeboid forms of *Blastocystis* sp. subtype 3. Acta Derm Venereol. 2008;88:80-1.

43. Vogelberg C, Stensvold CR, Monecke S, Ditzen A, Stopsack K, Heinrich-Gräfe U, et al. *Blastocystis* sp. subtype 2 detection during recurrence of gastrointestinal and urticarial symptoms. Parasitol Int. 2010;59:469-71.

44. Hameed DM, Hassanin OM, Zuel-Fakkar NM. Association of *Blastocystis hominis* genetic subtypes with urticaria. Parasitol Res. 2011;108:553-60.

45. Zuel-Fakkar NM, Abdel Hameed DM, Hassanin OM. Study of *Blastocystis hominis* isolates in urticaria: a case-control study. Clin Exp Dermatol. 2011;36:908-10.

46. Zaglool DA, Khodari YA, Othman RA, Farooq MU. Prevalence of intestinal parasites and bacteria among food handlers in a tertiary care hospital. Niger Med J. 2011;52:266-70.

47. Bálint A, Dóczi I, Bereczki L, Gyulai R, Szűcs M, Farkas K, et al. Do not forget the stool examination!-cutaneous and gastrointestinal manifestations of *Blastocystis* sp. infection. Parasitol Res. 2014;113:1585-90.

48. Lepczyńska M, Chen WC, Dzika E. Mysterious chronic urticaria caused by *Blastocystis* spp.? Int J Dermatol. 2016;55:259-66.

49. Kantardjiev V, Galev A, Broshtilova V. Urticaria associated with amoeboid forms of *Blastocystis* spp. Asian J Res Infect Dis. 2019;2:1-4.

50. Vezir S, Kaya F, Vezir E, Karaosmanoğlu N, Adiloğlu AK. Evaluation of intestinal parasites in patients with chronic spontaneous urticaria in a territory hospital in Turkey. J Infect Dev Ctries. 2019;13:927-32.

51. Kanani A, Betschel SD, Warrington R. Urticaria and angioedema. Allergy Asthma Clin Immunol. 2018;14:59.

52. Dionigi PC, Menezes MC, Forte WC. A prospective ten-year follow-up of patients with chronic urticaria. Allergol Immunopathol. 2016;44:286-91.

53. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133:1270-7.

54. Clark CG. Extensive genetic diversity in *Blastocystis hominis*. Mol Biochem Parasitol. 1997;87:79-83.

55. Kaneda Y, Horiki N, Cheng XJ, Fujita Y, Maruyama M, Tachibana H. Ribodemes of *Blastocystis hominis* isolated in Japan. Am J Trop Med Hyg. 2001;65:393-6.

56. Poirier P, Wawrzyniak I, Vivarès CP, Delbac F, El Alaoui H. New insights into *Blastocystis* spp.: a potential link with irritable bowel syndrome. PLoS Pathog. 2012;8:e1002545.

57. Abdel-Hameed DM, Hassanin OM. Proteaese activity of *Blastocystis hominis* subtype3 in symptomatic and asymptomatic patients. Parasitol Res. 2011;109:321-7.

58. Vassalos CM, Spanakos G, Vassalou E, Papadopoulou C, Vakalis N. Differences in Clinical Significance and Morphologic Features of *Blastocystis* sp Subtype 3. Am J Clin Pathol. 2010;133:251-88.

59. Berrilli F, Di Cave D, Cavallero S, D'Amelio S. Interactions between parasites and microbial communities in the human gut. Front Cell Infect Microbiol. 2012;2:141.

60. Stensvold CR, Clark CG. Current status of *Blastocystis*: A personal view. Parasitol Int. 2016;65:763-71.

61. Yan Y, Su S, Lai R, Liao H, Ye J, Li X, et al. Genetic variability of *Blastocystis hominis* isolates in China. Parasitol Res. 2006;99:597-601.

62. Valsecchi R, Leghissa P, Greco V. Cutaneous lesions in *Blastocystis hominis* infection. Acta Derm Venereol. 2004;84:322-3.

63. Demirci M, Yildirim M, Aridogan BC, Baysal V, Korkmaz M. Tissue parasites in patients with chronic urticaria. J Dermatol. 2003;30:777-81.

64. Deng L, Wojciech L, Gascoigne NRJ, Peng G, Tan KSW. New insights into the interactions between *Blastocystis*, the gut microbiota, and host immunity. PLoS Pathog. 2021;17:e1009253.

65. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med. 2016;375:2369-79.

66. Nabizadeh E, Jazani NH, Bagheri M, Shahabi S. Association of altered gut microbiota composition with chronic urticaria. Ann Allergy Asthma Immunol. 2017;119:48-53.

67. Stensvold CR, van der Giezen M. Associations between gut microbiota and common luminal intestinal parasites. Trends Parasitol. 2018;34:369-77.

68. Lu T, Chen Y, Guo Y, Sun J, Shen W, Yuan M, et al. Altered gut microbiota diversity and composition in chronic urticaria. Dis Markers. 2019;2019:6417471.

69. Mannucci C, Casciaro M, Minciullo PL, Calapai G, Navarra M, Gangemi S. Involvement of microRNAs in skin disorders: A literature review. Allergy Asthma Proc. 2017;38:9-15.

70. González-Guarda R. The syndemic orientation: implications for eliminating Hispanic health disparities. Hisp Health Care Int. 2009;7:114-5.

71. The Lancet (ed). Syndemics: health in context. Lancet. 2017;389:881.

72. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet. 2017;389:941-50.

73. Mendenhall E, Newfield T, Tsai AC. Syndemic theory, methods, and data. Soc Sci Med. 2022;295:114656.